of conformational motion and discuss some simplified cases. In principal will be shown that in a case of first approximation when the field equation holds good with cosmological constant than macromolecular surfaces undergo to vibrational motion and the frequency of such oscillations directly depends on Ricci scalar. In another words when linear configuration of Einstein tensor and metric tensor is proportional to energy stress tensor then equation of conformational motion reduces to simplified equation similar to Hooke's low rewritten in tensorial form and has well defined mathematical solution. Correspondingly the question why biological macromolecules do not have single energetic minimums and fluctuate among many energetic minimums will be answered.

352-Pos Board B121

pH-Dependent Free Energy Landscape, Conformational Selection, and Thermodynamics of Protein Folding

Wookyung Yu, **Iksoo Chang**.
Center for Proteome Biophysics, Department of Physics, Pusan National University, Busan, Korea, Republic of.

Protein conformation change depending not only on the values of temperature, denaturant concentration but also on the values of solvent pH. The difference of the pH-denaturation from the thermal or urea denaturation is that hydrogen atoms (un)bind exclusively to R, K, Y, C, H, D, E amino acids. Thus the pH effect on the protein conformation is selective so that the physico-chemical machinery for the biological function of a protein frequently has its origin due to the solvent pH. Although several previous approaches were suggested to elucidate the (un)protonation behavior of a protein conformation, those were mainly oriented on evaluating pKa values of titratable residues in a given static protein conformation. The theoretical and calculation framework for describing the effect of solvent pH to the thermodynamic and kinetic properties of proteins under the equilibrium fluctuation is indispensable for the fundamental understanding of important biological phenomena of proteins.

Here we present a development of the pH-dependent free energy function of proteins incorporating its equilibrium fluctuations based on the concept of statistical physics. The validity of our approach is justified by reproducing the experimental pKa values of titratable residues in several proteins. We also present the analytical and calculation framework for describing the pH-dependent thermodynamics and folding kinetics of proteins by the exact calculation. The effects of pH not only on the free energy landscape but also on the folding characters of several proteins are discussed.

353-Pos Board B122

Functional Properties of HIV1 Reverse Transcriptase from Normal Mode Analysis with Elastic Networks and Essential Dynamics

Adam S. Goler, James A. Brozik, David J. Keller.
Washington State University, Pullman, WA, USA.

All DNA Polymerases possess similar spatial features, functional properties, and have similar discrete state kinetic mechanisms to describe function. One of the fundamental goals in biophysics is to predict the mechanism, and eventually, the dynamics of protein function, from purely structural information. To this end, normal mode analysis is a well-established first step. In fact, the lowest frequency normal modes of proteins often correspond to the largest amplitude conformational changes, and are thus likely to play a dominant role in a protein's functional properties. We have both qualitatively and quantitatively explored the low frequency modes for the enzyme HIV1 Reverse Transcriptase, with and without DNA bound to the polymerase active site, using an Elastic Network model. We then compared the Elastic Network modes to those calculated from Essential Dynamics of nanosecond scale all-atom molecular dynamics simulations. From these comparisons we have isolated specific large amplitude modes of the protein corresponding to the fingers closing, in addition to other torsional oscillations, and assess equilibrium states for both free polymerases as well as those bound with dsDNA.

354-Pos Board B123

Exploring Macromolecular Machine Motions

Jose Ramon Lopez-Blanco, Erney Ramirez, Santiago Garcia, **Pablo Chacon**.
Institute of Physical Chemistry CSIC, Madrid, Spain.

Normal modes in internal coordinates (IC) furnish an excellent way to model functional collective motions. Here we present an enhanced version of our versatile NMA-IC framework, iMod (1). Even though the complexity reduction obtained from the IC and the employ of coarse-grained (CG) representations, the diagonalization step remained as a bottleneck for large macromolecular machines. Now, virus, long F-actin filaments or large microtubules can be studied with moderate CG representations by solving the large-scale eigenvalue problem on shared-memory multiprocessors using ad doc algebra procedures. Also, new parameterization of the elastic model has been done to improve the overall conformational flexibility description. By extending its applicability to larger systems and by improving elastic network potentials, we expedite the study of the collective conformational changes of such biological relevant complexes and their functional implications.

1.López-Blanco JR, Garzón JI, Chacón P. (2011) iMod: multipurpose normal mode analysis in internal coordinates. Bioinformatics. 27 (20): 2843-2850.

355-Pos Board B124

Conformational Dynamics of Ras Isoforms: Specificity at the Catalytic Domain

Nandini Rambahal, Aleyamehu Gorfe, Harrison Hocker.
UTHSC Houston, houston, TX, USA.

Ras proteins serve as crucial signaling modulators in cell proliferation through their ability to hydrolyze GTP and cycle between GTP ''On'' and GTP ''off'' states. There are four different human Ras homologues and the sequence homology is almost conserved at the catalytic domain. These homologues differ in their ability to activate different effectors and hence different signaling pathways. Much of the previous work on Isoform specificity has attributed this difference to the HVR region of Ras proteins which dictates its localization in the membrane. In this work, we have analyzed the specific dynamics in the catalytic domain of two Ras Homologues H-ras and K-ras to probe for alterations in the active site architecture that could possibly provide effector and modulator specificity to the different isoforms. We explored the conformational dynamics between of WT H-ras and K-Ras proteins and compared the conserved communications and residue interactions between these two proteins at the catalytic domain. We have also studied the dynamics of a transforming mutant of H-ras and K-ras and an effector selective??? mutant of H-ras. Preliminarily analysis revealed that there is a distinct conformational distribution for K-ras and H-ras, including in the functionally important switch regions. Collectively we have determined that wild type K-ras is more dynamic than H-ras and that the structure of the effector binding loop more closely resembles that of the T35S Raf-selective mutant, providing new insight into the mode of effector specificity at the catalytic domain. Furthermore we have determined that specific mutations in H-ras and K-ras perturb the conformational equilibrium differently.

356-Pos Board B125

Detailed Conformational Changes Involved in TopoII DNA Binding, Bending and Cleavage

Ahmet Mentes.
UC Irvine, Irvine, CA, USA.

We have used Molecular Dynamics (MD) simulation methods and two analytical approaches(the Gaussian Net- work Model(GNM) and Anisotropic Network Model (ANM)) to investigate the structural and energetic details of the S.cerevisiae topoII during the first step of its catalytic cycle. At the initial state of the first step of its catalytic cycle, the protein and 34 bp straight-DNA structure have no interaction. At the final state of the cycle, we have the bended-DNA/TopoII complex where the protein binds to DNA. The results show that DNA-gate and C-gate opening/closing mechanism causes the DNA-bending before the DNA G- gate cleavage. There is strong agreement between the theoratical and the experimental DNA-bending results where its global bending is $\approx 150^{\wedge}0$.The results also show that there is a hysteresis between DNA-bending and gate openings/closings. The transition of 3 helices on Winked Helix Domain during DNA bending and cleavage states has been also investigated because this transition might be important for the T-segment DNA passage through the G-Segment DNA. Normal mode analysis is additionally used to characterize the functional flexibity of the protein,especially C-gate domain closing/opening during the DNA binding process and before its cleavage.The Plastic Network Model(PNM) is also used to generate a conformational change pathway for S.cerevisiae topoII based on two (C-gate closed and open) crystal structures. PNM connects the energy basins corresponding to known two crystal structures at their lowest common energies. Analysis of PNM provides an identification of hinge motion upon DNA binding/bending. We also showed that 'trapdoor' mechanism causes faster closing of C-gate domain of the protein than the closing of the same domain without TYR residue upward motion. Because of its clinical importance, our study may provide new insight into the dynamics and structure of TopoII-DNA complex.

357-Pos Board B126

Conformation-Switching in Adenylate Kinase Revisited with a Path-Ensemble Simulation

Sundar Raman Subramanian, Daniel M. Zuckerman.
University of Pittsburgh, Pittsburgh, PA, USA.

Adenylate kinase (ADK), which reversibly converts ATP and AMP to two ADP molecules, has two conformational states, inactive (open) and active (closed); crystal structures of both states were solved in mid 1990s. Numerous studies using experiments as well as computer simulations have aimed to elucidate the relationship between conformational rearrangement and ADK function.